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Modeling Cost-Effectiveness of Cervical Cancer Screening in Hungary

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A B S T R A C T

Objectives: Our aim was to compare the cost-effectiveness of two national cervical cancer screening programs aiming to involve those who do not regularly participate in the screening program in Hungary with no screening, using a public health-care payer's perspective and a 20-year time horizon. **Methods:** We built a Markov model based on disease progression. The health-care costs of screening and treatment were received from real-word data. Other input data were obtained from the literature. The cost-effectiveness of the current screening program (a screening test that combines cytology and colposcopy in gynecological outpatient services) and of a planned new screening program (only cytology, and Pap smear is taken locally by public health nurses), both supported with a more active communication campaign, were compared with no screening. **Results:** The incremental cost-effectiveness ratio of the intensified current screening practice was $33,100 per quality-adjusted life-year compared with no screening, whereas the incremental cost-effectiveness ratio of the renewed program was $18,990 per quality-adjusted life-year compared with no screening. The most influential parameters in the deterministic analysis were the quality-of-life weights of undetected stage I or IIA cancer. In the probabilistic sensitivity analysis, 99.9% of the simulations were below the incremental cost-effectiveness ratio of $30,000 per quality-adjusted life-year in the case of the renewed strategy. **Conclusions:** Providing services closer to the population is a rational economic option for the reform of the Hungarian cervical cancer screening program. The other policy aspects of this development, human resource need, stakeholders' interests, organizational aspects, and attitude of the target population need to be carefully considered.

Keywords: cost-effectiveness, economic models, Hungary, mass screening, uterine cervical neoplasms.

Introduction

The mortality of cervical cancer is comparatively high in Hungary: the crude death rate was 7.9 per 100,000 women in 2008 [1]. An organized cervical cancer screening program was launched for women aged 25 to 65 years in 2003 as part of the National Public Health Program. Women were invited to undergo cervical screening every 3 years. The method of screening followed the long-standing Hungarian professional tradition of opportunistic screening; it included Papanicolaou test and colposcopic examination performed by gynecologists in outpatient services located in cities. Although data about the participation rates are somewhat contradictory, one can conclude that 50% to 60% of women aged 25 to 65 years regularly visit a gynecologist and undergo cervical screening without any organized program. Over 7 years, the organized screening program did not significantly increase the proportion of the regularly screened population [2,3].

The National Public Health and Medical Officers' Service (NPHMOS), which is responsible for the organization of the screening program, realized the inefficiency of the system and performed pilot projects to develop a new strategy. In one of the pilot projects, public health nurses were trained to obtain a cervical smear and they provided the service locally, even in small villages. The program targeted marginalized populations and did not include colposcopic examination. The promising results regarding the quality of the service and participation of the population made this method a potential option for reform of the national program. Our study aimed to estimate the cost-effectiveness of different cervical screening programs in Hungary to support health policy decision making.

Methods

We developed a cohort simulation Markov model in Microsoft Excel. Although several models of the cost-effectiveness of cervical screening programs have been published [4–6], none was directly suitable for our research question on the cost-effectiveness of the different methods to increase participation of those Hungarian women in cervical screening program who would not use this health service otherwise (i.e., not using opportunistic screening). It

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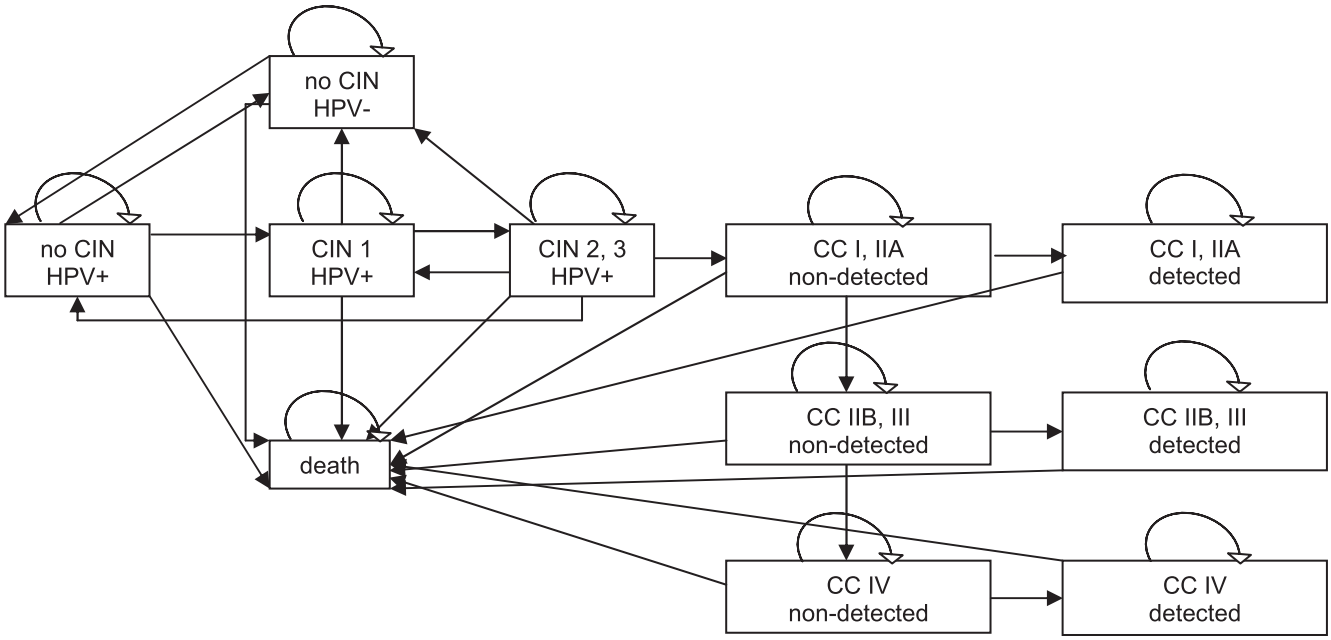

Fig. 1 – Health states of the disease progression model. CC, cancer; CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus.

was either not possible to rebuild previously published models or all relevant aspects of the Hungarian screening strategies (e.g., use of colposcopy) were not possible to be modeled.

Model structure

We adopted, modified, and rebuilt a previously published model [7]. Like other published models, this model was not suitable for all aspects of the Hungarian screening program, but we could use the core part of the model about disease progression. The original model was based on disease progression and also contained health states of low-risk human papilloma virus (HPV) infections, which we did not include in our model. The simplified model we actually used is presented in Figure 1. The boxes of the figure represent health states, and the arrows represent transition routes between health states. Cervical intraepithelial neoplasia (CIN) is precancerous alteration of the cervix epithelium. These changes might be benign or infectious in nature, but the more advanced alterations are at high risk of transforming to cancer. The "cancers detected" states are modeled in two separate states, "newly detected" (3 months after detection) and "treated," to account for the differences in quality of life (QoL) and immediate and long-term costs. The model estimates the lifespan of women (aged 25–64 years) on the basis of participation in regular screening. The model is split into 5-year age cohorts. On the basis of incidence rates from the literature [8], we calculated the transition probabilities for the cycle length of 1 month by using constant incidence rate assumption. For example, at age 35 to 39 years, the incidence rate from CIN 2, CIN 3, and HPV+ state to cancer I and IIA nondetected state was estimated at 0.022 per person-year. Assuming constant incidence rate, the estimated 1-month risk, the transitional probability can be calculated as follows:

$$\text{risk}_{1\text{ month}} = 1 - e^{-0.022\times(1/12)} = 0.001832$$

The current prevalence of different stages was estimated by using published data [5,9,10]. We attached QoL weights to each health state (Table 1). The age-specific QoL weights in the general population were taken from the Hungarian National Health Survey 2000 [11]. The QoL weights of undiagnosed and treated cancer are expert estimations, whereas the QoL weights of newly diagnosed cancers in different stages were taken from the literature [8].

To confirm the calibration of our model, we compared the predicted number of newly diagnosed cervical cancer cases in case this population was not involved in the screening program, as is the case currently, with the number of new cervical cancer cases reported in the National Cancer Registry in 2007.

Different disease stages may be diagnosed at certain probabilities depending on the characteristics of the screening test (Table 2) [4,7,12–14]. P1 to P5 stands for Papanicolaou classification of the cervical smear cytology from "normal" to "invasive cancer" [12]. According to current Hungarian practice, if a person has a P3 cytology result, she receives a combination local anti-inflammatory treatment and the cytology is repeated within 2 weeks. If the subsequent result is P3 or worse again, then conization is offered just like for those who had a P4 or P5 result initially. If the subsequent result after an initial P3 cytology is P2, then the cytology is repeated again in 6 months. If this result is P1 or P2, then the patient returns to the regular screening regimen. If the result is worse than P2, conization is offered.

The effect of early detection and treatment was modeled in such a way that if someone undergoes a conization, then she is

Table 1 – Quality-of-life weights* corresponding to different cancer stages.

	Nondetected	Newly detected	Treated
CC I-IIA	1.0 (0.1000)	0.68 (0.0680)	0.95 (0.0950)
CC IIB-III	0.95 (0.0950)	0.56 (0.0560)	0.75 (0.0750)
CC IV	0.9 (0.0900)	0.48 (0.0480)	0.60 (0.0600)

The numbers in parentheses are the standard errors applied for the distributions in the probabilistic sensitivity analysis.
CC, cancer.
* The age-specific quality-of-life weights are multiplied with these weights.

Table 2 – The default setting of the distribution of the screening test results according to the disease stages and the screening method.

Test result	Only cytology					Cytology and colposcopy				
	Normal	CIN 1	CIN 2 and 3	CC I	CC II-IV	Normal	CIN 1	CIN 2 and 3	CC I	CC II-IV
P1-P2	0.95	0.517	0.472	0.286	0	0.31	0.1	0.04	0.01	0
P3	0.04	0.448	0.493	0.286	0	0.621	0.45	0.48	0.04	0
P4-P5	0.01	0.035	0.035	0.428	1	0.069	0.45	0.48	0.95	1

CC, cancer; CIN, cervical intraepithelial neoplasia.

moved back to the initial health stage of no CIN and no HPV infection.

The effect of cancer treatment is reflected in the model by stopping the progression of cancer if it is detected. Nevertheless, the cancer treatment was not assumed to be 100% effective, because the mortality rates in the detected cancer states were much larger than the corresponding age-specific mortality rates.

The discount rates of cost and quality-of-life years (quality-adjusted life-year [QALY]) are user input in the model. In the default model, we used 5% for both, which is in line with the current Hungarian guideline of health economic evaluations [15]. Our analysis was conducted from the public health-care payer's perspective.

Cost data

Resource utilization data of the screening process was estimated per protocol: resource units were multiplied by the tariffs of the National Health Insurance Fund (NHIF) for the services. The costs of the Pap smear (NHIF procedure code: 14720), the cytological examination (NHIF procedure code: 42700), and gynecological screening examination (NHIF procedure code 16631 plus 42600) were \$0.68, \$11.82, and \$11.27, respectively. The price of local anti-inflammatory treatment was \$5.80. The cost of the conization was \$1390.6. The cost of conization was calculated by the cost of the diagnosis-related group "operation of uterus and adnexum of uterus due to in situ carcinoma and nonmalignant disease" coded as 643B. Costs of care in different stages of cervical cancer were calculated from real-world data. Patients with different stages of newly diagnosed cervical cancer in 2006 at the Clinics of Obstetrics and Gynecology at the University of Debrecen and at the Department of Gynecology and Obstetrics at the Saint Stephen Hospital were identified. The patient's social security number was matched with individual resource utilization and payment records in the NHIF database. The NHIF was one of the participants in the research consortium led by the Institute of Healthcare Quality Improvement and Hospital Engineering, commissioned by the Ministry of Health. The total health-care cost by cancer stage in respect to time after the diagnosis was calculated from aggregated payment records (Table 3). It included acute and chronic inpatient care, outpatient care, imaging (computed tomography and magnetic resonance), home care, and drug costs.

The cost of traveling was included among the costs, because it is reimbursed to the screening participants by the NHIF. The cost of traveling can be set in the model; the default value (\$7.40) was based on the average distance from outpatient services in the disadvantaged areas. If the screening is done locally, then the number of examinations performed on each occasion can also be set. The default value is set to 20. In this case, the traveling cost per examination is only \$0.37 because it is the service provider who needs to travel.

The organizational cost of the screening program can also be set. Based on the information we received from the NPHMOS, the default value for one round of the screening program was set to \$666,000 per 1.7 million people (the currently unscreened population from age 25 to 64 years). In addition, the cost of \$1.48 per person was calculated for direct communication. The cost of the training of public health nurses was estimated as \$74,000 per year on the basis of data of the NPHMOS.

The model calculates cost in Hungarian forint (HUF). In this article, we used the purchasing power parity exchange rate of 135 HUF per dollar rate, which eliminates differences in price levels between countries [16].

We did not consider indirect costs in the analysis.

Strategies modeled

Many strategies can be modeled according to the different combinations of the input parameters. One can set the time interval of the screening examination (2 or 3 years), the method of screening (locally, cytology only, or cytology combined with colposcopy in outpatient services), and the target participation rate by age group.

The model compares the total QALYs and the total costs expected in 20 years in the target population if the specified screening program is performed or if there is no screening. It calculates costs and QALYs by age cohorts, the weighted average of these, and an extrapolated value for the population involved. Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the cost difference with the difference in QALYs.

In this analysis we compared two scenarios to no organized screening. In Scenario 1, the current practice of screening by cytology and colposcopy in outpatient services by gynecologists continues, and it is supported more actively (e.g., increased presence on mass media, letters, information leaflets, involvement of local opinion leaders, and general practitioners) than the current communication campaign to reach and motivate the target population. In Scenario 2, the Pap smear is performed by trained public health nurses locally in the offices of the general practitioners. In this case, colposcopic examination was not included. Based on policy discussions and a pilot study, this is the most likely strategy to improve the Hungarian national cervical screening program. The same communication support was assumed in this scenario. We assumed that because of the communication efforts 50% participation rate would be achieved in all age groups by both scenar-

Table 3 – Direct medical cost (\$) per month of cervical cancer by stages and time after the diagnosis.

Stage	Time after the diagnosis			
	Months 0-3	Months 4-12	Months 13-24	From month 25
CC I-IIA	1076 (268.98)	201 (50.27)	147 (36.64)	92 (22.99)
CC IIB-III	1076 (268.98)	329 (82.32)	315 (78.63)	263 (65.63)
CC IV	1076 (268.98)	327 (81.75)	416 (104)	305 (76.25)

The numbers in parentheses are the standard errors applied for the distributions in the probabilistic sensitivity analysis.
CC, cancer.

Table 4 – The estimated number of new cervical cancer cases and the actual number of cases registered in the National Cancer Registry.

Age group (y)	Age cohort weight in the population (%)	Estimated number of cases in the first year	Registered number of new cases in 2007
25–34	27	15 (12–18)	108
35–44	23	69 (56–84)	220
45–54	26	218 (184–265)	278
55–64	24	241 (199–291)	218
25–64	100	543	824

The numbers in parentheses are the range of the values obtained in the probabilistic sensitivity analysis.

ios; that is, 50% of those who had not been screened regularly would be involved.

We performed deterministic and probabilistic sensitivity analyses. We tested how robust the results were to ±10% change of the input parameters. In the probabilistic sensitivity analysis, we defined distributions for the key input parameters and conducted 5000 Monte Carlo simulations with sampling from these distributions. Gamma distributions were applied for incidence rates of transitions, participation rates, cancer stage–specific mortality, stage-specific health-care costs, and organizational costs of screening. Beta distributions were applied for participation rates in screening and QoL weights of cancer states. Dirichlet distributions were applied for the initial prevalence figures of the different health states and for the proportions of screening test results according to the disease state. We plotted the results on an acceptability curve.

Results

Our model was undercalibrated in the young age groups, and it was well calibrated above age 44 years; that is, the number of the estimated new cases with no further development of the screening program was consistent with the actual incident cases registered in the National Cancer Registry (Table 4). When interpreting this finding, one needs to consider that some cervical cancer cases occur in the screened population as well; thus, not all the reported cases are expected to occur among women who do not regularly undergo screening. Table 5 shows the cost and the QALYs corresponding to the two scenarios and no screening. Both screening strategies were cost-effective if we consider that three times the GDP/inhabitant ratio ($58,700) is the informal threshold of cost-effectiveness. The health gain was larger in Scenario 1 than in Scenario 2 by 1025 QALYs for the population. However, the extra cost of this was substantial: $86.8 million. The ICER of Scenario 1 compared with that of Scenario 2 was $84,564 per QALY, far beyond the informal cost-effectiveness threshold.

Table 6 shows the dependence of cost-effectiveness on the age of the participants. The data show that even in the case of the more cost-effective Scenario 2, the ICER is lower than the informal cost-effective threshold only above 30 years of age.

Decreased discount rate and later starting age of the screening program considerably decreases the ICER. On the other hand, increasing the frequency of the screening greatly increases the ICER, that is, makes the screening much less cost-effective (Table 7). Figure 2 shows how the cost-effectiveness of the two strategies depends on the participation rate. It can be seen that the curves reach a kind of asymptote; the ICERs do not change much above the participation rate of 50%.

The results were robust to the uncertainty of 10% change in the most influential input parameter, QoL weights of undetected stage I or IIA cancer, which did not change the ICER of Scenario 2 more than $3500 per QALY (Fig. 3). The variability of the results in the probabilistic sensitivity analysis is presented in Table 5 together with the point estimates. All simulated results were situated in the northeast quadrant of the cost-effectiveness planes (figures not shown). The cost-effectiveness acceptability curve of Scenario 2 shows that 99.9% of the simulations provided an ICER below $30,000 per QALY, whereas only 72% of the simulations produced an ICER below this level in case of Scenario 1 (Fig. 4).

Discussion

The organized cervical cancer screening program that started in 2003 has not fulfilled the expectations; it has not significantly increased the proportion of the regularly screened population in Hungary. The main reasons for this failure are service organization (gynecological outpatient services in cities) and ineffective communication [3]. Results from health surveys show that the

Table 5 – Cost-effectiveness of the different screening scenarios.

	Scenario 1	Scenario 2	No screening
Cost ($) per person	297 (237–352)	171 (123–222)	67 (38–95),* (38–123)†
QALYper person	11.1740 (10.9399–11.3581)	11.1725 (10.9614–11.3658)	11.1670 (10.9375–11.3403)* (10.9570–11.3510)†
ΔCost ($) per person	230 (199–256)	104 (86–136)	Reference
per population	157,862,382	71,096,011	
ΔQALY per person	0.00695 (0.00239–0.01773)	0.00546 (0.00443–0.01476)	Reference
per population	4769	3744	
ICER ($ per QALY)	33,100	18,990	Reference

The numbers in parentheses are the range of the values obtained in the probabilistic sensitivity analysis.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
* When it was compared with Scenario 1.
† When it was compared with Scenario 2.

Table 6 – The cost-effectiveness of the screening strategies compared with no screening in the different age groups.

Age group (y)	ICER ($ per QALY)	
	Scenario 1	Scenario 2
25–29	116,969	64,799
30–34	73,687	37,929
35–39	38,898	22,073
40–44	31,187	17,952
45–49	26,077	15,071
50–54	24,480	14,266
55–59	24,764	14,544
60–64	25,628	15,175

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

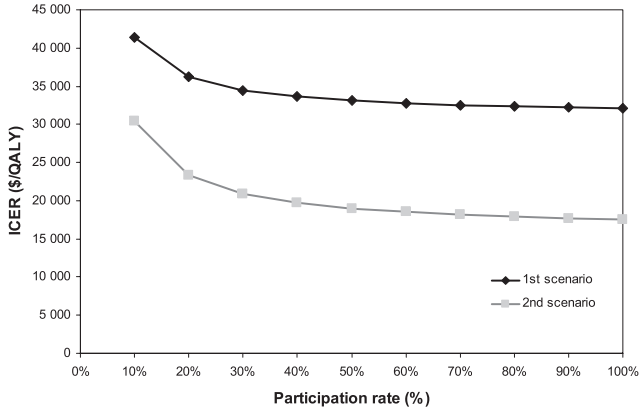

Fig. 2 – The relationship between the incremental cost-effectiveness ratio and the participation rate by screening strategy. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

majority of women who do not use cervical screening services are less educated women in smaller communities. Opportunistic and organized screening occurs at higher rates in big cities. The NPHMOS, the organization responsible for the management of the national screening programs, is currently working on the reform of the cervical screening program. It has launched pilot projects to test how bringing the service closer to the target population works. The initial results were promising with the involvement of specially trained public health nurses performing Pap smears locally in the general practitioners' offices. Furthermore, NPHMOS is to launch large-scale communication programs about cancer screening, including the cervical cancer screening program, and it also supports local, more personalized communications. Our study was part of the process of collecting evidence supporting the reform of cancer screening programs. The two potential scenarios studied were the intensified current program (i.e., the current screening program with a more efficient communication) and renewing the methodology of the screening (performing Pap smears locally by public health nurses and using only cytology without colposcopy) together with a more efficient communication.

Our results showed that the newly planned strategy is more cost-effective than the intensified present program compared with no screening. Furthermore, the intensified current strategy is not cost-effective compared with the new strategy; thus, the planned development is reasonable from the health economic point of view. Another important result was that neither screening strategy was cost-effective under the age of 30 years; there is very limited room for health gain in this age group because of the low incidence of the disease. However, when interpreting this finding, one needs to take into account that our model was undercalibrated under the age of 45 years. If the reported high incidence in young women is valid, and all these cases occur among unscreened women, then the potential health gain by screening is higher in these age groups; thus, the screening is more cost-effective than as we estimated.

Our results regarding the cost-effectiveness of the new strategy are conservative because of another reason as well. We assumed that the same participation rate could be achieved with the same investment in communication. Nevertheless, on the basis of the results of some pilot projects, we can assume that a higher participation rate could be achieved with the same per capita investment by the involvement of local opinion leaders and local communication campaigns. If the participation rate were increased to 70% from the default 50% in Scenario 2, then the ICER comparing this strategy to no screening would decrease from $18,990 per QALY to $18,169 per QALY.

Like any health economic model, ours is also prone to uncertainties of the model structure and its parameters. We used the best available evidence, tested the calibration of the model, and used sensitivity analysis to test the robustness of our conclusions. The number of new cervical cancer cases estimated by the model was in accord with the actual number of cases reported in the National Cancer Registry above age 44 years. The results were sensitive for the length of the screening interval. Decreasing the interval to 2 years would proportionally increase the cost more than the health gain; the ICER would thus increase considerably. Like the cost-effectiveness of many other preventive measures, the cost-effectiveness of cervical cancer screening is also sensitive to the discount rate applied. Because the current investment will produce health benefits only in the long run, the high discount rate devalues the benefit more than the cost.

Regarding the screening examination itself, we modeled the current Hungarian practice. Although the current official Hungarian guidelines recommend changing the cytology classification to the Bethesda system, the majority of current practices still use the Papanicolau classification; therefore, we used the latter in our

Table 7 – The effect of major input parameters on the cost-effectiveness of the screening strategies compared with no screening.

	Scenario 1			Scenario 2		
	ΔQALY	Δcost ($)	ICER ($ per QALY)	ΔQALY	Δcost ($)	ICER ($ per QALY)
Default (in Table 5)	0.00695	230	33,100	0.00546	104	18,990
Discount rate 3%	0.00911	267	29,280	0.00718	120	16,646
Frequency of screening 2 y	0.008	361	45,114	0.00678	167	24,629
Starting age 35 y	0.00791	217	27,432	0.00618	100	16,095

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

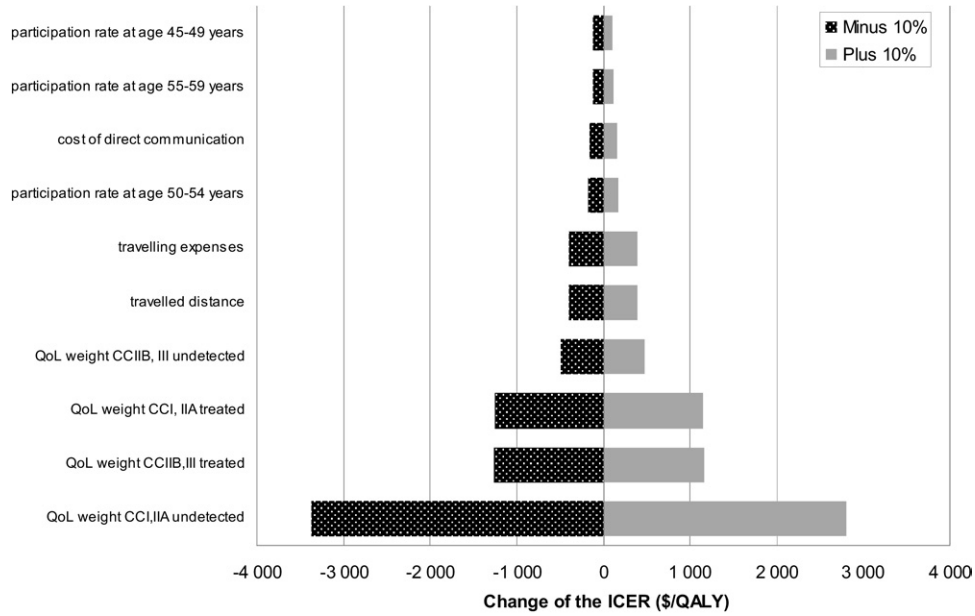

Fig. 3 – Sensitivity of the cost-effectiveness of Scenario 2 to ±10% change in the most influential input parameters. CC, cancer; ICER, incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; QoL, quality of life.

model. Moreover, HPV testing is part of the screening protocol in many countries, but this is not the case in Hungary. Therefore, we did not include HPV testing in the model.

A limitation of our study is that the cost estimation of cervical cancer was based on data of only two health centers. Nevertheless, they provided care for more than 10% of patients with newly diagnosed cancers; thus, the sampling size was reasonably large. We selected a general hospital from the capital and a university clinic from the country. Nonetheless, the sample cannot be considered a representative sample. This, however, could not largely bias our results, because gynecologists follow the national guideline in the care of cervical cancer patients [17]. Furthermore, we tackled this problem in the sensitivity analysis. Our cost estimates are still the best available, because they are stage-specific ones. The optimal solution—having a random sample of all new cervical cancer cases—was not feasible in our study.

The cost-effectiveness of cervical screening was already assessed in Hungary in 2003 [18]. In that economic evaluation, authors assumed that increased screening participation of women aged 25 to 65 years could prevent 19.6% to 38.4% of mortality from cervical cancer over 10 years in Hungary according to the different scenarios analyzed. Treatment costs of cervical cancer were not calculated according to cancer stages. The economic evaluation was based on the assumption that increased cervical screening participation did not change the national treatment cost of cervical cancer; therefore, incremental costs were attributable only to the increased cost of screening. The incremental cost of screening divided by the avoided death cases resulted in 16.6 to 33.8 million HUF per life gained. On the basis of a British study, the authors assumed that one avoided death case could result in 23 additional life-years [19]; therefore, one life-year gain can be achieved at 0.7 to 1.5 million HUF incremental cost. As the methodology and the assumptions of that cost-effectiveness analysis, especially the calculation of life-years gained and the constant treatment cost, were subject to criticism, the Ministry of Health initiated an economic evaluation of intensified cervical screening in a disease state economic model under the leadership of the Institute of Healthcare Quality Improvement and Hospital Engineering. The project presented in this article included the development of an economic model and a cost estimation study based on individual medical and resource utilization records of patients in different cancer states selected from two major medical centers.

Opportunistic cervical cancer screening has a long tradition in Hungary. The organized cervical cancer screening program needs to target women who otherwise would not utilize this service. Our results showed that moving the service closer to the population is a cost-effective strategy.

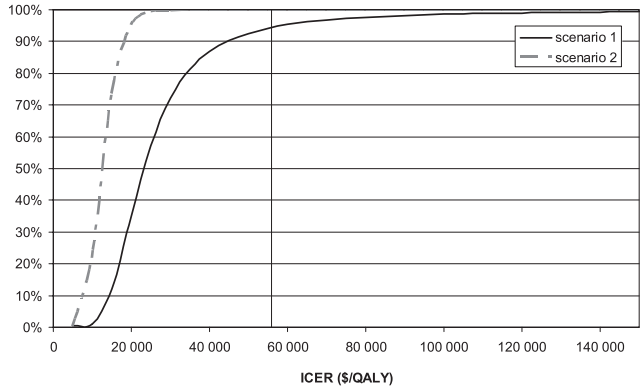

Fig. 4 – The cost-effectiveness acceptability curve of Scenario 1 and Scenario 2 compared with no screening. The straight line represents Scenario 1, the dotted line Scenario 2, and the vertical line represents the informal Hungarian cost-effectiveness threshold of $55,800 per QALY. QALY, quality-adjusted life-year.

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